REMARKS

As a result of the foregoing amendment, the claims have been amended in a manner which is believed overcomes the various rejections under the first and second paragraphs of 35 USC 112. In particular, those terms which are objected to have been removed from the claims. In particular, the word "substantially" has been deleted from the claims. The expression "target cell specific portion" has been amended to read "portion for binding to a specific target cell".

Claim 14 has been amended to add the recitation that the variant is a constituitively active caspase with apotopsis inducing activity. In addition, the objected to expression cytotoxic portion has been amended to read a cytotoxic portion conjugated to a portion specific for binding to a cell.

Reconsideration and withdrawal of each of the formal rejections based on the foregoing amendments is requested as they are no longer relevant.

However, it is noted that the examiner has stated that it is not clear that the target cell specific portion and the cytotoxic portion are conjugated together. There's more than adequate support for the recitation that the portions are conjugated together and additionally, if the cytotoxic and target cell specific portions were not conjugated together, the cytotoxic portion cannot be internalized into the cell.

In addition, with respect to the examiner's objection that the claims to a target cell specific portion and any constituitively active caspase would have the necessary structure to confer apototic activity, it is noted that a definition of the caspase having such activity is found in the summary of the invention at page 3, line 18 to page 7, line 4. Furthermore, a test for apototic activity is described in example H of the application.

As to the examiner's assertion that the specification does not provide sufficient support to make and use the invention recited in claims 21 and 22, page 37 discloses the use of the compound in making pharmaceutical compounds and provides more than ample sufficient information regarding excipients and carriers to allow one with ordinary skill in this art to apply the common general knowledge to make such a pharmaceutical composition. In fact, the Johnstone and Thorpe citations which were cited as rendering claim 21 obvious clearly teach one that it is common practice to formulate such pharmaceutical compositions.

The examiner has also objected that only the in vitro killing of cells has been disclosed and alleges these results cannot be extrapolated to an in vivo situation. There is no evidence that shows in vitro results will not be repeated in an in vivo situation in the context of the present invention. Indeed, the experimental data for in vitro testing of the present invention is highly successful, e.g., a poorly internalized antibody (anti-CEA)

still produces 75% killing in vitro. Therefore, more readily internalized antibodies should be even more effective in vitro and there is no reason that the internalization of the antibody would be impaired in vivo. In addition, the examiner's citation of the '894 patent shows that in vitro and in vivo internalization of the disclosed immunotoxin occurs and cell death is effective is both experimental models. All of the evidence shows that success in vivo situations can reasonably be extrapolated from the in vitro dated. Accordingly, these objections should be withdrawn.

The examiner has rejected claims 1 and 2 as being unpatentable under 35 USC 102 over the '313 patent. This reference is directed to a US 5,994,313 is directed at a chimeric monomer comprising a "receptor" domain and an "action" domain (column 3 lines 12-16). The "action domain" is able to produce apoptotic activity on a least two monomers have been oligomerised by an .introduced non-peptide based ligand that binds to the receptor domain of each monomer (column 3 lines 46-56).

The apoptotic compound of US 5,994,313 is not constitutively active, as administration of a ligand 'is required in order for apoptotic activity to occur (column 3 lines 46-56). The phrase "constitutively active" as used in the claims of the present application is defined in the specification of the present application as being "a caspase in an activated form " or "a precursor of an active caspase that can spontaneously self-catalyse to the active caspase " (page 10 lines 5 to 10)

Furthermore, the receptor domain of US 5,994,313 binds to the administered ligand and is not "specific for binding to the target-cell" (column 11, lines 36-42). As such, the compound of US 5,994,3 13 does not disclose the compound claimed in Claim 1 of the present application.

The action and receptor domains of each chimeric monomer are fused in US 5,994,313 (column 3 lines 10-16). However in order to obtain apoptotic function a non-covalent linkage is required (column 7 lines 4-7) between at least two chimeric monomers and the administered ligand. As such the functional molecule is not a single compound as claimed in the present application.

Instead, US 5,994,313 appears to disclose a specific mixture/complex of compounds that only produce an effect when they interact in non-covalent manner. The presently claimed compound is a single recombinant or chemically fused compound/protein.

The method of US 5,994,313 requires genetic engineering of cells and is stated to be primarily -for use as a "kill-switch" in the control of gene therapy cells (column 3, lines 1-9 and column 12 lines 24-29). This design and proposed application is substantially different from the protein delivery approach taken by the present inventors.

The invention of US 5,994,313 is disclosed in columns 7-8 and 12 to be useful for genetically engineering cells to possess a kill switch. The engineered cells can be

used to produce a desired product or action (either in vitro or in vivo) and then, by addition of the oligomerising ligand, those cells which express internally the chimeric proteins described in US 5,994,313 will be killed. The presently claimed invention is directed to the killing of target cells by the addition of the active protein compound not a gene therapy approach which was advocated in the art when the invention was made.

In columns 3-4 of US 5,994,313, the action domain is described as being selected from "any proteins or protein domains which trigger apoptosis upon cross-linking". This definition does not include the caspases of the present invention as the caspases of the present invention do not require any such cross-linking in order to be active, i.e. they are constitutively active.

The action domain of US 5,994,313 is only capable of triggering apoptosis, via signalling cascade. Such cascades may be blocked or missing cascade members in cancer cells due to cellular changes due to the cancer. Therefore, the action domain of US 5,994,313 may not work.

Hence, the caspases of the presently claimed invention are novel over US 5,994,313.

Accordingly, rejection on this basis is untenable and should be withdrawn.

103 Reconsideration and withdrawal of claim 21 as being obvious over the Johnstone and Thorpe reference when taken with the '313 patent is also improper and should be withdrawn. As noted above, the compound disclosed in the '313 patent is not that of the present invention. Consequently, combining the compound of the '313 patent with the method of formulating as disclosed in Johnstone and Thorpe would not produce the pharmaceutical composition of claim 21. Clearly, this rejection of claim 21 should be withdrawn.

103 Reconsideration of the rejection of claims 1, 3, 10-16, 21-22 over the Srinivasula, et al. article in view of the '894 patent and Colussi, et al. are requested. The '894 patent discloses an immunotoxin comprising an antibody specific for binding to breast cancer cells and the toxin Ricin A. The Ricin A toxin is well known to kill cells. The mechanism of action of Ricin A is described in Medical Aspects of Chemical and Biological Warfare - Chapter 32 (1997) Ed. Brig. Gen. R. Zajtchuk, M.C., U.S. Army. Office of the Surgeon General, Dept. of the Army, U.S.A (in particular p634 Pathogenesis).

Briefly, Ricin A specifically and irreversibly inactivates the 28S ribosomal subunit of eukaryotic ribosomes, thereby preventing protein synthesis. The prevention of protein synthesis is what causes the death of the cell.

By comparison, the action of the constitutively active caspases of the present invention is more direct and more extensive. Caspases kill cells by, for example, actively cleaving and disrupting chromosomal DNA, the cytoskeleton and multiple enzymes (see specification page 5 lines 7 to 24).

Therefore, the skilled person would recognise that caspases e.g. those disclosed in Srinivasula (1998) work in a completely different way to Ricin A. The skilled person would not consider it obvious to replace the Ricin A of the immunotoxin of US 4,753,894 with caspases as described in Srinivasula because the two: groups of compounds are not equivalent.

The examiner states that Colussi (1998) teaches that fusion of procaspase-3 to the caspase 2 domain confers dimerisation of procaspase molecules and converts pro-caspase 3 to an autoactivating caspase capable of inducing apoptosis.

By the same token, Colussi therefore discloses that oligomerisation is essential for activation (constitutive or otherwise) of caspases including caspase 3. This disclosure teaches away from the presently claimed invention of which an essential feature is that constitutively active caspases are used and these require no oligomerisation in order to be activated. Therefore, a skilled person could not arrive at the presently claimed invention when combining Colussi with any other citation.

Srinivasula (1998) discloses constitutively active caspase 3 and caspase 6. However, Srinivasula only teaches that the constitutively active caspases may be considered for use in targeted gene therapy, i.e. the gene for the constitutively active caspase is introduced into a target cell (page 10110, right column, last paragraph). The gene based approach disclosed in Srinivasula is at odds with the protein based approach of the Ricin A containing immunotoxin of US 4,753,894. Therefore, combination of Srinivasula with any other document could not produce the presently claimed invention.

Additionally, at the priority date of the present application it was in the field that gene delivery was the only mode of delivery of caspases which could reasonably be expected to succeed, taking into account the need for cell specificity and efficient delivery to intracellular sites (since the expression product of the delivered gene is inevitably at an intracellular site).

Within the art at the priority date (and subsequently) there existed a technical prejudice away from delivery of enzyme prodrug systems in the form of a protein (antibody) and towards delivery in the form of genetic material. This is evident from a number of references.

Within the field of site-specific enzyme and toxin delivery a range of compounds had been studied and all of these studies regard genetic delivery methods as superior to protein delivery. For example:

Gene therapy involving caspase has been disclosed in Marcelli, M. et al. (1999) Cancer Res. 59, (382-390). This shows a genetic delivery of caspase to prostate cancer cells in order to induce apoptosis as a therapeutic measure. There is no suggestion within the document that any future work on the directed targeting of caspase would involve delivery of caspase in the form of a protein. The authors discuss the future of using adenovirus transfer and more specific promoters, thereby teaching skilled persons that the way forward lies in the use of improved vectors for delivery of genetic material encoding caspase.

Hay, M.P. et al. (1999) Bioorg. Med. Chem. Lett. 9, (2237-2242) made a direct comparison between gene and protein delivery with E. coli nitroreductase, an enzyme which activates the prodrug 2-nitroimidazol-5ylmethyl carbamate. Tumour cells were incubated with the protein form of the enzyme and in a separate experiment, transfected with the gene for the enzyme. The prodrug had a 10-fold increase in cytotoxicity in the protein delivered cell, and 21-fold increase in cytotoxicity in the gene delivered cells, suggesting gene deliver is sLiperior.

Vallera, D.A. et al. (February 2000) Cancer Res. 60, (976-984) made a direct comparison between gene and protein delivery using an IL4diphtheria toxin (IL 4-DT) fusion protein. The IL 4 receptor is found on some leukemia cells. When used in vivo in a murine tumour model, the IL 4-DT fusion protein injected i.v. did not protect against tumour growth (at a maximum tolerated dose), whereas transfected T cells (IL 4-DT gene delivered with a retrovirus) were able to produce enough fusion protein in vivo to give protection. In addition, there was no systemic, renal or hepatic toxicity with the gene delivered approach. In this example, gene delivery worked because it led to higher expression of the recombinant therapeutic protein.

In addition, there are a number. of references that have been published since the priority date of this application, that relate to caspase delivery as an antitumour therapy. These show a continuing technical prejudice towards genetic delivery of enzymes and toxins. For example:

Shariat, S.F. et al. (2001) Cancer Res. 61, (2562-2571) investigated caspase-based suicide gene therapy using Adenoviral vectors. They concluded future work should focus on improving the vectors for genetic delivery of caspase.

Shinoura, N. et al. (2000) Hum. Gene Ther. 11, (1123-1137) reported studies involving adenovirus-mediated gene therapy using a caspase-8 encoding DNA whose expression was under the control of the myelin basic protein promoter, a tissue-specific promoter. They suggested that future work would lie in the creation of novel adenovirus gene therapy vectors and using better cell specific promoters.

Komata, T, et al. (2001) Cancer Res. 61, (5796-5802)reported treatment of malignant glioma cells by gene therapy involving the use of a genetic construct encoding constitutively active caspase - 6, the expression of which is under the control of the human telomerase reverse transcriptase gene promoter which is predominantly active in tumour cells.

Clearly, these documents show that since the priority date of the present application, the technical population continues to have a prejudice toward gene delivery based methods. Consequently, one with skill in this art would not consider the disclosure of a possible gene therapy approach with a protein delivery approach since there was not reasonable expectation that such an approach would work. Indeed, applicants attempted protein delivery approach and found that a fusion protein according to the present invention can effectively induce apoptosis (see page 58, lines 1-6). This result is quite surprising in view of the understanding in the prior art that only gene delivery should be considered. In fact, the result is even all the more surprising given that the fusion protein was targeted to CEA, which is a target cell antigen known not to internalize effectively (see page 58, lines 8-13). This further demonstrates that the constituitively active caspase is internalized very effectively. The prior art simply contains no appreciation of this property. In addiiton, the present invention provides molecules that bind to even more readily internalized targets than CEA which would thus provide even a higher apoptotic activity.

Accordingly, the claims are not rendered obvious over the combination of these references and this rejection should be withdrawn.

Applicants include herewith copies of the documents discussed above in an appropriate IDS.

In view of the foregoing, it is submitted that this application is in condition for allowance and favorably reconsideration and prompt notice to that effect are earnestly solicited.

Respectfully submitted,

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